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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,190	12/09/2001	Richard A. Dixon	NBLE:026US	2623

7590 07/14/2004

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EXAMINER	
KALLIS, RUSSELL	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/936,190	DIXON ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *20-49 and 55-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-19,50-54,67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The restriction of 3/24/2004 is hereby VACATED in view of the following restriction requirement.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-19, 50-54 and 67-69, drawn to a first method, of introducing into a plant species an enzyme catalyzing conversion of a flavanone to an isoflavanone by transforming a plant to express the DNA encoding said enzyme; a transformed plant, seed and progeny thereby; and a method of using the transformed plant to prepare a nutraceutical composition.

Group II, claim(s) 20 and 22-23, drawn to a second method, of synthesizing an isoflavanone intermediate or an isoflavanone from a flavanone in a bacterial, fungal, algal or insect cell system.

Group III, claim(s) 21 and 38-40 drawn to a third method, of reducing levels of isoflavanoid compounds in a naturally isoflavanoid producing plant or plant cell by introduction of antisense or silencing constructs containing an intact or fragment of a CYP93C gene.

Group IV, claim(s) 24-29, 32-37 and 41-49 drawn to a first product, a naturally non-isoflavanoid producing plant cell, a naturally isoflavanoid producing plant cell transformed with a DNA segment encoding an enzyme that catalyzes aryl migration of a flavanone to an isoflavanone intermediate or an isoflavone and the isolated DNA segment encoding a P450 of the CYP93 family that catalyzes the aryl migration of a flavanone to yield an isoflavanone intermediate or an isoflavone and a protein encoded by the isolated gene.

Group V, claim(s) 55, drawn to a fourth method, of producing a pharmaceutical composition using a transgenic plant transformed with an isolated gene or DNA segment

which encodes a cytochrome P450 that can catalyze the aryl migration of a flavanone to yield an isoflavanone intermediate or an isoflavone.

Group VI, claim(s) 56-58, drawn to drawn to a fifth method, of using a transgenic plant transformed with an isolated gene or DNA segment which encodes a cytochrome P450 that can catalyze the aryl migration of a flavanone to yield an isoflavanone intermediate or an isoflavone, having an increase in the level of an isoflavonoid, to provide a nutraceutical benefit by administering said isoflavonoid.

Group VII, claim(s) 59-66, drawn to a sixth method, for transforming a plant with an isolated gene or DNA segment which encodes a cytochrome P450 that can catalyze the aryl migration of a flavanone to yield an isoflavanone intermediate or an isoflavone; wherein the level of an isoflavonoid, the nutritional value, the disease resistance, the bacterial and fungal symbiosis, or the nodulation efficiency is increased.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of a method of introducing into a plant species an enzyme catalyzing conversion of a flavanone to an isoflavanone of Group I is not shared with the method of synthesizing an isoflavanone intermediate or an isoflavanone from a flavanone in a bacterial, fungal, algal or insect cell system of Group II; the method of reducing levels of isoflavanoid compounds in a naturally isoflavonoid producing plant or plant cell using antisense or silencing constructs of an intact CYP93C gene of Group III; the naturally non-isoflavanoid and naturally flavanoid producing plant cells transformed with a DNA segment encoding the enzyme that catalyzes aryl migration of a flavanone to an isoflavanone intermediate or an isoflavone of Group IV; the method of producing a pharmaceutical composition of Group V; or the method of transforming a plant with an isolated gene or DNA segment which encodes a cytochrome P450 that can catalyze the aryl migration of a flavanone to yield an isoflavanone intermediate or an isoflavone of Group VI.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Upon election of Group I, II, III or IV, Applicant is required to elect a single nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 4. This requirement is not to be construed as a requirement for an election of species, since each of the nucleic acid

sequences or amino acid sequences recited in alternative form is not a member of a single structurally and functionally related genus, but rather constitutes an independent and patentably distinct invention. Separate searches and considerations would be required for examination of each of the nucleic acid sequences.

Applicant is reminded that since SEQ ID NO: 4 was not disclosed in U.S. provisional 60/123,267 filed March 8, 1999; claims drawn to SEQ ID NO: 4 have priority dating back only to the filing date of PCT US00/05919 filed March 8, 2000.

During a telephone conversation with Applicant's representative Robert Hanson on 6/15/2004 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-19, 50-54 and 67-69. The traversal is on the ground(s) that SEQ ID NO: 1 and 4 are limitations in dependent claims and that they are both sequences from leguminous species that are structurally related to each other. The Examiner acknowledges Applicant's argument and will agree to search SEQ ID NO: 1 and 4. Affirmation of this election must be made by applicant in replying to this Office action. Claims 20-49 and 55-66 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-69 are pending and Claims 1-19, 50-54 and 67-69 are examined.

Claim Rejections - 35 USC § 112

Claims 1-19, 50-54 and 67-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims a method of introducing into a plant species an enzyme catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or an isoflavone by transformation of the plant with a DNA segment, wherein the DNA segment comprises a CYP93C gene, a Medicago truncatula homolog of a CYP93C gene, SEQ ID NO: 1, or SEQ ID NO: 4; and a method of increasing the isoflavonoid level in a naturally isoflavonoid producing plant by transformation with an enzyme catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or an isoflavone.

Applicant describes SEQ ID NO: 1 encoding an isoflavone synthase from soybean that catalyzes the aryl migration of a flavanone to form an isoflavanone intermediate or an isoflavone; and SEQ ID NO: 4, a cytochrome P450 polynucleotide classified according to structure, but undefined with respect to function or enzymatic activity.

Applicant does not describe an enzyme catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate other than the enzyme encoded by SEQ ID NO: 1.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of nucleic acid sequences falling within the scope of the claimed genus of polynucleotides that catalyze the aryl migration of a flavanone to form an isoflavanone intermediate. Applicants only describe a polynucleotide of SEQ ID NO: 1 shown to catalyze the aryl migration of a flavanone to form an isoflavanone intermediate or an isoflavone. Applicants fail to describe structural features common to members of the claimed genus of nucleic acids and structural features common to those sequences catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or isoflavone. Further, at the time of the effective filing date the function of the category of cytochrome P450 enzymes classified as CYP93C was unknown in the art.

Furthermore, given the lack of description of the necessary elements essential for catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or isoflavone, it remains unclear what features identify an isoflavone synthase. Since the genus of polynucleotides or DNA segments catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or isoflavone as claimed has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*.

Claims 1-19, 50-54 and 67-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of production of the isoflavonoid genistein in plants that do not normally produce isoflavonoids using SEQ ID NO: 1 and for a method of increasing the production of isoflavonoids in plants that normally produce isoflavonoids (i.e. legumes) using SEQ ID NO: 1, and plants thereof,

does not reasonably provide enablement for a method of production of the isoflavonoid daidzein in plants that do not normally produce isoflavonoids using SEQ ID NO: 1; or a method of production of the isoflavonoid daidzein in plants that do not normally produce isoflavonoids using SEQ ID NO: 4 or a CYP93C uncharacterized with respect to function, or for a method of increasing the production of the isoflavonoid genistein in plants that normally produce isoflavonoids by transformation with a poynucleotide of SEQ ID NO: 4 or any CYP93C encoding polynucleotide other than SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are broadly drawn to a method of introducing into a plant species an enzyme catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or an isoflavone by transformation of the plant with a DNA segment, wherein the DNA segment comprises a CYP93C gene, a Medicago truncatula homolog of a CYP93C gene, SEQ ID NO: 1, or SEQ ID NO: 4; and a method of increasing the isoflavonoid level in a

naturally isoflavonoid producing plant by transformation with an enzyme catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or an isoflavone.

Applicant teaches SEQ ID NO: 1, a CYP93C encoding an isoflavanone synthase, isolated from soybean and characterized as catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or an isoflavone in transformed insect cells (page 21), the transformation of *Arabidopsis* SEQ ID NO: 1 (CYP93C isolated from soybean encoding isoflavone synthase), wherein the transformed plants produce the isoflavanoid genistein (pages 23-24), and SEQ ID NO: 4 isolated from Medicago truncatula classified as a cytochrome P450 CYP93C protein (page 21).

Applicant does not teach the activity or functional expression of SEQ ID NO: 4 isolated from Medicago truncatula in any cell system or the functional expression of any CYP93C other than SEQ ID NO: 1 or the transformation of any other plants other than *Arabidopsis* using any other sequence other than SEQ ID NO: 1.

The state of the art for isolating and deducing cytochrome P450 enzymatic activity from structure alone is unpredictable because of the limited knowledge of enzymatic activity for cytochrome P450 subfamily members available in the art. For example, the isolation from Medicago truncatula of cDNA classified as P450 81E subfamily members showed affinity for the same substrates but produced different products when expressed in yeast. (Liu C. *et al.* The Plant Journal, 2003; Vol. 36 pp.471-484; see abstract and page 473 column 2, the entire column).

Further, the state of the art for producing any number of isoflavanoids in non-isoflavanoid producing plants is unpredictable because enzymes such as chalchone isomerase in non-leguminous plants do not use isoliquiritigenin and therefore expressing

an enzyme that catalyzes the aryl migration of a flavanone to form an isoflavanone intermediate or isoflavone in a non-leguminous plant would not result in the conversion of liquiritigenin to daidzein. Furthermore, the researchers did not report the production daidzein in the non-leguminous *Arabidopsis* species when transformed with the leguminous sequence encoding isoflavone synthase from soybean and chalcone isomerase from alfalfa suggesting that there are unforeseen mechanisms regulating flux through the flavanoid pathways in non-leguminous plants (Liu C. *et al.* PNAS, 2002, Vol. 99, No. 22; pp. 14578-14583; see page 14850, column 2 lines 26-37; and page 14581 Table 1).

Given the lack of guidance in the instant specification, undue trial and error experimentation would be required for one of ordinary skill in the art to isolate and screen through the multitude of non-exemplified CYP93C sequences, either by testing for aryl migration activity to form an isoflavanone intermediate or isoflavone in isolated transformed cells or in transformed plants, by HPLC analysis of isoflavanone intermediate or isoflavone in non-leguminous plants, and in transformed leguminous for increased isoflavoid production, in order to identify those sequences encoding an enzyme catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate as broadly claimed.

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is drawn to SEQ ID NO: 4 and is also dependent upon Claim 12 drawn to SEQ ID NO: 1. It is contradictory that the claim could be drawn to two different sequences and hence it is unclear what is being claimed.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 67-69 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed inventions encompass untransformed plants and seeds, which are a product of nature and not one of the five classes of patentable subject matter. Claims 67-69 are drawn to parts such as seeds and progeny of the transformed plant. Due to Mendelian inheritance of genes, a single gene introduced into a parent plant would only be transferred at most to half the male gametes and half the female gametes. This translates into only two thirds of the progeny having at least a single copy of the transgene and one quarter of the progeny would not carry a copy of the transgene. Since the claim encompasses progeny that lack the transgene, the claim encompasses plants and seeds that are indistinguishable from plants and seeds that would occur in nature. See *American Wood v. Fiber Distintegrating Co.*, 90 U.S. 566

(1974), *American Fruit Growers v. Brogdex Co.*, 283 U.S. 2 (1931), *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 33 U.S. 127 (1948), *Diamond v. Chakrabarty*, 206 USPQ 193 (1980).

All Claims are rejected.

Claims 1-19, 50-54 and 67-69 are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest a method of introducing into a plant species an enzyme catalyzing the aryl migration of a flavanone to form an isoflavanone intermediate or an isoflavone by transformation of the plant with a DNA segment of SEQ ID NO: 1, SEQ ID NO: 4, or a Medicago truncatula homolog of a CYP93C gene, and plants and seeds transformed with said polynucleotides; or a method of increasing isoflavanoid levels in a plant transformed with SEQ ID NO: 1, SEQ ID NO: 4, or a Medicago truncatula homolog of a CYP93C gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russell Kallis

Russell Kallis Ph.D.
July 9, 2004